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99 NOV -5 P12:38

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

November 5, 1999

Docket # 99D 2729

Gentlemen:

Attached are two copies of the National Pharmaceutical Alliance's Technical Committee's comments on the draft Guidance for Industry; BA and BE Studies for Orally Administered Drug Products - General Considerations. The closing date for comments was November 2, 1999 but we hope that these comments will be included with those received previously . We appreciate the opportunity to comment.

Very truly yours,

Robert a. Jemsi for

Christina Sizemore
President

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NPA's Technical Committee Comments on the FDA Guidance Document

Entitled:

BA and BE Studies for Orally Administered Drug Products – General Considerations - DRAFT GUIDANCE

Docket No. 99D-2729 November 5, 1999

General Comments:

1. As a whole, we wish to congratulate the Agency for developing this comprehensive guidance document. Since general guidances can never contain all of the combinations and permutations for different drugs, we encourage the Agency to continue developing drug product specific guidances to assist with the development of generic drug products.

2. We also commend the Agency for identifying the need to establish bioequivalence, using objective criteria, during the IND/NDA stages of product development. Often, for new chemical entities, the bioequivalence of the market image and clinical trial formulations may not meet the strict criteria established by the Office of Generic Drugs (i.e., confidence intervals within 80% and 125% for Cmax and AUC). Instead, the NDA Division Director may judge that the differences in bioavailability are "not clinically relevant". On Page 6, the Agency states that:

   > "Proper mapping of the dose-or concentration-response curve can be useful in situations where the drug product produces levels that are either higher or lower than the reference product. In the case where levels are higher, population clinical data accumulated with higher doses may be sufficient to demonstrate that the increase in plasma levels would not be accompanied by additional risk. Similarly, population clinical data gained with lower doses may be able to demonstrate that reduced levels of the test compared to the reference product are associated with adequate efficacy. In either event, the burden is on the sponsor to demonstrate the adequacy of the clinical trials database to cover these observed deviations."

   If the Agency "relaxes" the bioequivalence criteria for an NDA drug product, we recommend that the Agency include the data from the dose - or concentration response relationship in the Summary Basis of Approval. We also recommend that NDA holders identify and the Agency publish intrasubject variability. Other firms, that develop and market generic products after patent expiration, may then use these standards (developed and used by the pioneer for any postapproval changes).

Specific Comments:

1. Replicate Study Designs

   Page 8 of the guidance states: "Replicate study designs (see section IV) are recommended for all BE studies using pharmacokinetic measurements, with the following exceptions: (1) BE studies of drug products containing drug substances with long half lives (e.g., > 96 hours); (2) BE studies in which a steady-state design is needed; and (3) BE studies in which excessive blood collection and/or other safety factors would arise as a result of treatment replication. For BE studies conducted during the IND period, the recommendation applies only to BE studies between the to-be-marketed dose form and pivotal clinical trial batch material.

Additional justification for the use of nonreplicate study designs can be provided by sponsors and/or applicants."

We strongly object to this unnecessary study design. The Agency appears to be asking for the replicate design in order to evaluate individual bioequivalence (and the unvalidated subject-by-formulation interaction). This study design and the IBE concept is not needed for most drug products, since bioequivalence can be easily established using the standard 24 subject, 2-way crossover study design. For example, it doesn't make any sense to require replicate study designs for drug products with wide therapeutic ratios such as amoxicillin; because of its high safety margin, most patients receive either 250 mg or 500 mg doses and strict BE criteria would not make sense. Replicate study designs are necessary only for those drug products which have a high (>30%) intra-subject variability and a limited subject population. IBE may be useful for those drug products that would require more than 40-48 subjects in a standard two-way crossover design, but must be validated prior to inclusion in an Agency Guidance document.

2. Study Population: (Page 8)

The guidance states: "Unless otherwise indicated by a specific guidance, subjects recruited for in vivo BE studies should be 18 years or older and capable of giving informed consent. An attempt should be made to admit as heterogeneous a study population as possible, with a reasonable balance of males and females, young and elderly, and members of differing racial groups. Restrictions on admission into the study should be based solely on safety considerations. In some instances, it may be useful to admit patients into BE studies for whom a drug product is intended. In this situation, sponsors and/or applicants should attempt to enter patients whose disease process is stable for the duration of the BE study."

We are concerned with the very wide inclusion criteria specified by the Agency. We agree, in concept, that the volunteer population should mimic (as closely as possible) the patient population. We are concerned, though, that this will increase the study variability and will require an increase in the number of subjects necessary to meet BE criteria.

The purpose of the BE study is to test the bioequivalence of the test and reference products under a controlled environment. Removal of the controls that the Agency has developed over the past 20 years, will certainly increase study variability (which will increase the number of subjects and therefore the cost to manufacturers). Also, we wish to point out that it is very difficult to recruit elderly "healthy volunteers", since many elderly are patients and receive at least one concomitant medication. In the past, concomitant medications cause an individual to be excluded from study participation.

The Agency should better define the requirement for a "reasonable balance of males and females, young and elderly, and members of differing racial groups." As mentioned earlier, elderly are very difficult to recruit. Also, the balance of racial groups is dependent on the geographic location of the study clinic. In our opinion, it will be impractical to place any restrictions on the demographics of study participants. Such restrictions will cause unnecessary delays in the conduct of BE trials. The task of balancing the study participants becomes impossible when studies requiring two or more groups are required. For these multiple group studies, the Agency should elaborate on the necessity that all groups be equally balanced for each of these demographic categories.

Finally, the Agency should address other inclusion and exclusion criteria in this section. For example, what weight range is acceptable (-10% to +15%, or is +20% to 25% acceptable)?

What, if any, concomitant medications are permitted in healthy volunteer studies? Generally 50% of the female population wishing to participate in BE studies are taking oral contraceptives. Are topical drug products allowed? Many people are taking multivitamins and "natural" drug products. Would these be permitted? Are smokers permitted to participate? If so, do smokers have to refrain from smoking during dosing days or during the washout period(s)?

3. Single-Dose/Multiple-Dose Studies (Pages 8-9)

We agree with the Agency's opinion that multiple dose BE trials are not sensitive indicators of bioequivalence. Generally, these study designs do not provide any additional information that is not provided by single dose fasting studies. However, exceptions to this rule are sometimes necessary. For example, some drugs may only be given to patients. Clozapine, for example, required a steady-state BE design due to safety concerns in healthy volunteers. In this case, schizophrenic patients were dosed with their "maintenance dose" under steady-state conditions and crossed-over to the test or reference product. It would have been unethical to wash these patients out in order to administer single doses of drug.

4. Pharmacokinetic Measures of Systemic Exposure (Pages 9-10)

a. Early Exposure

The Agency has proposed that early exposure in a product quality BA study can be assessed by measuring the partial AUC with a cutoff at the peak time (Tmax) of the reference formulation in each subject. This metric has not been properly validated as a useful metric for BE studies. It has been a research tool in the past and has been evaluated by the Agency using "simulated data". We recommend that the Agency include this metric and its assessment in PQRI. We also recommend that the Agency consider the effect of partial AUC values when the test product consistently has an earlier Tmax. In this case, the partial AUC of the test product will contain additional area due to elimination and not to absorption.

b. Peak Exposure

We agree with the Agency's continued assessment of peak exposure which is assessed by measuring the peak drug concentration (Cmax) obtained directly from the data without interpolation.

c. Total Exposure

The Agency recommended two metrics for total exposure: AUC(0-tlast) and AUC(0-infinity). We agree with the use of AUC(0-infinity), but not with AUC(0-tlast). The latter metric is study design dependent. This metric should only be presented in order to show that at least (on average) 80% of the AUC is accounted by AUC90-tlast).

5. Pharmacodynamics Studies (Page 10)

The Agency stated that "With an acceptable pharmacodynamic endpoint, suitably validated pharmacodynamic methods can be used to assess product quality BA and BE. This approach is usually not applicable to orally administered drug products where the drug is absorbed into the systemic circulation."

We urge the Agency to continue research (using PQRI) on methods to evaluate the

bioequivalence of oral drugs that are not absorbed into the systemic circulation.

6. Comparison of BA Measures In BE Studies (Pages 11-12)

The Agency stated the following: "This guidance recommends that certain in vivo BE studies conducted for (1) INDs, (2) NDAs, (3) ANDAs, and (4) amendments and supplements to NDAs and ANDAs be conducted using replicate designs (see section III.A.4). Sponsors may analyze their data using either average or population BE criteria (INDs and NDAs) or average or individual BE criteria (ANDAs and supplements to NDAs and ANDAs), provided the choice is specified in the study protocol prior to study initiation. At the sponsor's discretion, scaling may be used to judge BE when either an individual or population BE criterion is specified. Where a replicate fasting study is infeasible, sponsors are encouraged to contact appropriate review staff. In specified circumstances, replicate study designs are not needed (see III.A.4)."

As mentioned earlier, we strongly object to the use of replicated designs for all studies (except as noted in III.A.4) and the use of unvalidated pharmacokinetic methods (IBE). Replicate design studies and the use of IBE (after validation) should only be used for those drug products in which the innovator has demonstrated the need within their NDA. The need would be demonstrated either by a high intrasubject variability or a steep dose (or concentration) response curve.

7. DOCUMENTATION OF BA AND BE – C. Immediate-Release Products: Capsules and Tablets - 1. General Recommendations (Page 13)

The Agency recommended the following: "For BE studies for immediate-release dosage forms where the drug product contains a narrow therapeutic range drug (see section VI.F), this guidance recommends the following: (1) where an average BE criterion is selected, use of a BE limit of 90-111 percent for AUC; (2) where an individual BE criterion is selected, reference scaling is recommended, regardless of the variability of the reference listed drug."

(1) We disagree with the recommendation that reference scaling be used for IBE with NTI drugs, "regardless of the variability of the reference product". Reference products with small variability will potentially penalize excessively the test product in any bioequivalence study. This recommendation should be evaluated carefully before inclusion in this guidance. Additionally, the use of $\epsilon = 0$ should be evaluated and validated by the PQRI prior to inclusion in the guidance. Such restrictive criteria should be evaluated to demonstrate whether they would routinely indicate that two lots of a reference product are not bioequivalent.

(2) The Agency's suggestion of a narrower BE limit (i.e., 90 – 111) for narrow therapeutic drugs is appropriate. We also suggest that the Agency maintain a list of all narrow therapeutic drugs coming off of patent within any 5 year period.

(3) With regard to IBE, we again strongly recommend that the Agency delete any reference to this concept until PQRI data are generated which validates the IBE methodology, and determine either that a new BE criteria is necessary or determines a limited number of drug products which require this new method.

8. DOCUMENTATION OF BA AND BE – C. Immediate-Release Products: Capsules and Tablets - 2. Exposure Measurements (page 13)

We agree with the Agency's statement : "For orally administered, immediate-release drug products, BE may generally be established by measurements of peak (Cmax) and total

exposure (AUC)."

We also agree that occasionally, an innovator may establish, via clinical trials, that the rate of drug release from conventional/immediate release dosage form is clinically important. In these cases the use of an early exposure measure may be justified. However, the Agency should first validate any new metric before implementing its use for BE studies.

9. DOCUMENTATION OF BA AND BE – D. Modified-Release Products (pages 12 - 18)

Section 2. ANDAs: BE Studies (pages 16 – 17)

Agency Recommendation: For extended-release products submitted as ANDAs, the following studies are recommended: (1) a single-dose, replicate, fasted study comparing the highest strength of the test and reference listed drug product; and (2) a food-effect, nonreplicate study comparing the highest strength of reference and test products (section VI.A).

We agree that a single food-effect, nonreplicate study is necessary for modified release drug products; however, we disagree with the overall concept of requiring replicate design fasting studies for all drug products (immediate release and modified release).

Agency Recommendation: For drugs that exhibit nonlinear kinetics and/or drugs designated as narrow therapeutic range drugs (see section VI.F), this guidance recommends the following: (1) where an average BE criterion is selected, use of a BE limit of 90-111 percent for AUC; (2) where an individual BE criterion is selected, reference scaling is recommended, regardless of the variability of the reference product.

We disagree with the recommendation that nonlinear drug products be treated similarly to narrow therapeutic drug products. It makes sense to require a narrower confidence interval range for NTI drugs. However, a tighter requirement for all nonlinear drugs is unnecessary. Small differences in the in vivo release (and absorption) of nonlinear drugs will yield disproportionately large differences in bioavailability estimates. The purpose of a BE study is to establish that two dosage forms behave the same. The Agency should justify its reasoning for tightening these confidence intervals. The conventional confidence intervals (80 –120) are more appropriate for nonlinear drugs.

Finally, IBE criteria should not be included in this guidance until PQRI validates the methodology.

Section 3: Exposure Measurements (Page 17)

Agency Recommendation: "This guidance recommends that early and total exposure measurements be analyzed in single-dose studies for modified-release drug products."

We again disagree that early exposure measurements be used for all modified-release drug products. It was pointed out (in the section on immediate release dosage forms), that the innovator firm must first establish that the rate of release is clinically relevant. If not, then any early exposure metric is meaningless. Also, as we indicated earlier, the partial AUC metric should be validated (by PQRI) using "real data" and not just with pharmacokinetic simulations.

Section VI. SPECIAL TOPICS (Page 18)

A. Food-Effect Studies (Page 18)

We recommend that the Agency better define (in the draft guidance on food effect studies) those drug products that require food studies to be conducted as part of an ANDA. The current draft guidance basically requires a food study if the manufacturer can not establish that the tablet/capsule excipients do not affect drug absorption. In order to establish a lack of effect of excipients, generic manufacturers need to conduct an additional study comparing a solution and the solid oral dosage form. At best, two biostudies would still be required for a generic drug product. At worst, a third (postprandial) study will still be required.

B. Moieties to Be Measured (Page 18)

1. Parent Drug Versus Metabolites (Page 18)

The Agency has recommended that the moieties to be measured in BA and BE studies are the active drug ingredient or active moiety in the administered dosage form and, when appropriate, its active metabolites and/or degradants. For BE studies, determination of only the active moiety and/or active ingredient in the dosage form, rather than the metabolite, is generally recommended. The rationale for this recommendation is that the concentration-time profile of the active moiety in the dosage form is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination.

We agree with the concept of measuring only the parent drug for BE studies. Active primary and secondary metabolites do not need to be measured. The Agency should further elaborate on their definition of degradants and provide examples of drugs which fit this category. For example, one interpretation of this require the analysis of drug levels which are formed after hydrolysis of a prodrug. Also, the Agency should provide acceptance criteria for active metabolites (when required) and for the known degradants. Are the confidence interval criteria any different from those of conventional immediate release drug products?

2. Enantiomers Versus Racemates (Page 19)

We agree with the Agency's statement: "For BA studies, measurement of both enantiomers may be important. For BE studies, this guidance recommends measurement of the racemate using an achiral assay, without measurement of individual enantiomers."

We do not agree with the Agency's conditions as to when the individual enantiomers should be measured. As long as the manufacturer maintains the same ratio of enantiomers in the bulk drug substance, and as long as dissolution of the enantiomers is the same for the test product and the reference listed drug, differential enantiomer absorption will not be an issue. We also suggest that the Agency provide a list of those drug products which require enantiomer analysis. This information is not generally available in the literature nor is it available through FOI. Alternately, the Agency should assure that this information is present in the labeling for the reference listed drug product.

3. Drug Products With Complex Mixtures as the Active Ingredient (Page 20)

We agree with the Agency's recommendations in this section. In addition, the guidance should contain a target percentage that should be accounted for in biostudies. For example, if a complex drug mixture contains more than 8 components, but three components make up 90% of the potency, then only those three components should be assayed in BE studies.

C. Long Half-Life Drugs (Page 20)

We agree with the Agency's recommendations in this section. We would also reaffirm that replicate design studies should not be required for short or long half-life drugs. The Agency has not addressed the minimum number of subjects that should be included in parallel designs. This becomes especially important for those drugs tested in mixed populations of slow and fast metabolizers (for example, a drug metabolized primarily by CYP2D6). Although the Agency addressed AUC truncation for populations (and drugs) with high intersubject variability, the statistical power was not addressed. It is highly unlikely that drug products which exhibit a high level of intersubject variability will be able to meet current confidence interval criteria.

D. First Point Cmax (Page 20-21)

The Agency's approach to this problem is generally acceptable. However, the Agency may wish to increase the number of samples collected within the first hour from three to at least four or five. Fifteen minute intervals are not unreasonable nor are they a significant burden for phase I clinics. For example, protocols for products with a Tmax of 1 hour or less, should include sampling at 15, 30, 45, 60 and 75 minutes at a minimum.

E. Orally Administered Drugs Intended for Local Action (Page 21)

This section of the guidance appears to be purposely vague. Often, it is necessary to conduct a clinical efficacy trial to establish BE; for these cases, the Agency should address the statistical BE confidence interval criteria. Studies comparing active to active and attempting to prove BE require an inordinate number of subjects to meet current confidence interval criteria. Although firms may compare active to placebo and demonstrate efficacy, such studies have not been adequate to provide the firm with an "AB Orange Book rating".

F. Narrow Therapeutic Range Drugs (Page 21)

We recommend that, when an innovator's drug product meets the criteria for an NTI drug, that the Agency make this information available to the public. This could be provided as a list of NTI drug products on the CDER Internet Site or as an insert in the RLD labeling.

APPENDIX 2: General Pharmacokinetic Study Design (Pages 23 – 24)

Under Study conduct, we agree with all recommendations. The Agency should further elaborate on their recommendation that "the highest marketed strength should be administered as a single unit. If necessary for analytical reasons, multiple units of this highest strength can be administered, providing the total single-dose remains within the labeled dose range." Is there a maximum number of dosage units that may be administered when the analytical LOQ is difficult to achieve and safety is not an issue? Also, what is the Agency's definition of "adequate washout period"? Are 10 half-lives sufficient?

The Agency also recommends certain pharmacokinetic parameters that are not necessary (as discussed earlier in our comments). Specifically, the use of partial AUC values and IBE parameters (such as subject x formulation interaction) should not be included until appropriate validation is provided by PQRI.